(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 January 2007 (18.01.2007)

PCT

(10) International Publication Number
WO 2007/008156 A1

(51) International Patent Classification:
A61K 31/195 (2006.01) *A61K 9/20* (2006.01)
A61K 31/205 (2006.01) *A61P 3/10* (2006.01)

(21) International Application Number:
PCT/SE2006/000864

(22) International Filing Date: 10 July 2006 (10.07.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0501644-9 11 July 2005 (11.07.2005) SE

(71) Applicant *(for all designated States except US)*: **ASTRAZENECA AB** [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **BJÖRK, Seth** [SE/SE]; AstraZeneca R & D Södertälje, S-151 85 Södertälje (SE).

(74) Agent: **ASTRAZENECA**; Global Intellectual Property, S-151 85 Södertälje (SE).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

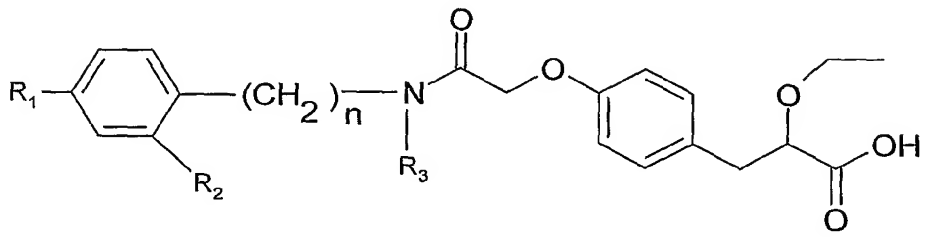
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2007/008156 A1

(54) Title: A PHARMACEUTICAL COMPOSITION COMPRISING A SUBSTITUTED PHENYLPROPIONIC ACID AS A FREE ACID AND AS TERT-BUTYL AMINE SALT THEREOF



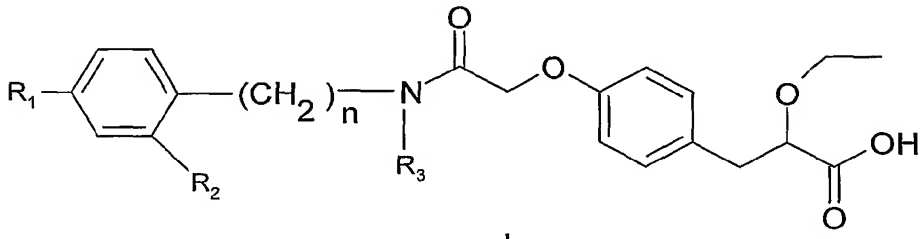
(I)

(57) Abstract: A pharmaceutical composition comprising a compound of formula I wherein n is 1 or 2, R^1 represents hydrogen, chloro, trifluoromethyl or trifluoromethoxy, R^2 represents hydrogen or fluoro and R^3 represents a C_{2-6}alkyl group, wherein the compound of formula (I) is present in the composition as a free acid and as a *tert*-butyl amine salt thereof.

A pharmaceutical composition comprising a substituted phenylpropionic acid as a free acid and as tert-butyl amine salt thereof

Field of the invention

The present invention relates to a pharmaceutical composition comprising a compound of formula (I)



I

wherein n is 1 or 2, R^1 represents hydrogen, chloro, trifluoromethyl or trifluoromethoxy, R^2 represents hydrogen or fluoro and R^3 represents a C_{2-6}alkyl group.

Background of the invention

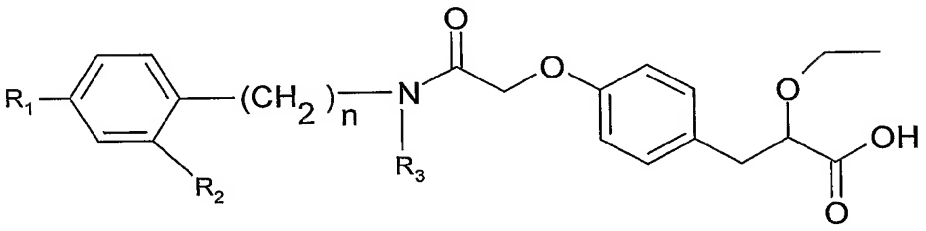
The metabolic syndrome including type 2 diabetes mellitus, refers to a cluster of manifestations including insulin resistance with accompanying hyperinsulinaemia, possibly type 2 diabetes mellitus, arterial hypertension, central (visceral) obesity, dyslipidaemia observed as deranged lipoprotein levels typically characterised by elevated VLDL (very low density lipoproteins), small dense LDL particles and reduced HDL (high density lipoprotein) concentrations and reduced fibrinolysis.

Recent epidemiological research has documented that individuals with insulin resistance run a greatly increased risk of cardiovascular morbidity and mortality, notably suffering from myocardial infarction and stroke. In type 2 diabetes mellitus atherosclerosis related conditions cause up to 80% of all deaths.

In clinical medicine there is awareness of the need to increase the insulin sensitivity in patients with the metabolic syndrome and thus to correct the dyslipidaemia which is considered to cause the accelerated progress of atherosclerosis. However, currently this is not a universally accepted diagnosis with well-defined pharmacotherapeutic indications.

PPAR is short for peroxisome proliferators activated receptor (for a review of the PPARs see T. M.Willson et al , J Med Chem 2000, Vol 43, 527). These compounds are effective in treating conditions associated with insulin resistance.

PPAR active compounds of formula (I)

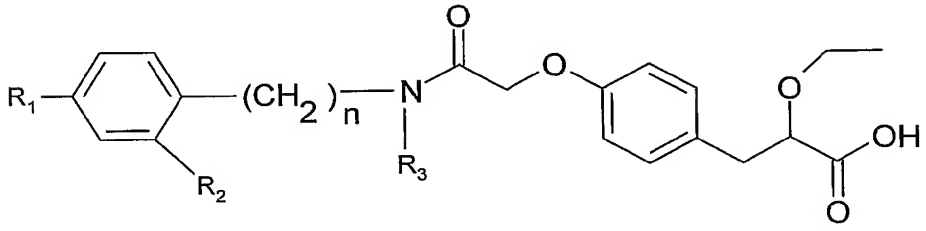


I

wherein n is 1 or 2, R^1 represents hydrogen, chloro, trifluoromethyl or trifluoromethoxy, R^2 represents hydrogen or fluoro and R^3 represents a C_{2-6}alkyl group, are as free acids sticky and hard to handle in tablet making. It has therefore been suggested to make salts thereof.

Description of the invention

The present invention relates to a pharmaceutical composition comprising a compound of formula I



I

wherein n is 1 or 2, R^1 represents hydrogen, chloro, trifluoromethyl or trifluoromethoxy, R^2 represents hydrogen or fluoro and R^3 represents a C_{2-6}alkyl group, wherein the compound of formula (I) is present in the composition as a free acid and as a *tert*-butyl amine salt thereof.

It has been surprisingly found that when making tablets from *tert*-butyl amine salts of the compound of formula (I) and exposing the salt to heat, the process results in tablets partially containing the free acid prepared *in situ*, thus providing a method to evade difficulties due to the sticky properties of the free acid during isolation and handling of said free acid for use in the

manufacture of pharmaceutical formulations. The salt may be exposed to heat, for instance, during a granulation phase or during compression of the tablets. One example of a process for achieving the composition according to the invention is to granulate and subsequently dry the granules.

According to one aspect of the invention, the amount of the *tert*-butylamine salt is equal to or below 95% of the total amount the compound of formula (I).

According to one aspect of the invention, the amount of the *tert*-butylamine salt is equal to or below 80% of the total amount the compound of formula (I).

According to one aspect of the invention, the amount of the *tert*-butylamine salt is equal to or below 50% of the total amount the compound of formula (I).

According to one aspect of the invention, n is 1 or 2 and R_1 and R_2 are hydrogen and R_3 is C_6H_{13}.

According to one aspect of the invention, n is 1, R^1 represents chloro, trifluoromethyl or trifluoromethoxy, R^2 represents H or fluoro and R^3 represents a C_{2-4}alkyl group.

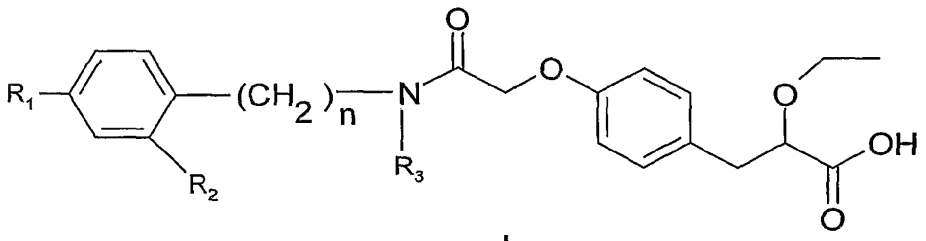
According to one aspect of the invention the pharmaceutical composition comprises a compound choosen from the following:
(2*S*)-2-Ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid;
(2*S*)-3-(4-{2-[Benzyl(hexyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid;
(2*S*)-3-[4-(2-{Butyl[2-fluoro-4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]-2-ethoxypropanoic acid;
(2*S*)-3-(4-{2-[(4-Chlorobenzyl)(ethyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid;
(2*S*)-2-Ethoxy-3-[4-(2-{ethyl[4-(trifluoromethoxy)benzyl]amino}-2-oxoethoxy)phenyl]-propanoic acid;
(2*S*)-2-Ethoxy-3-[4-(2-{ethyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl] propanoic acid; and
(2*S*)-3-[4-(2-{Butyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]-2-ethoxypropanoic acid
as a free acid and as a *tert*-butyl amine salt thereof.

According to one aspect of the invention, the dosage form is an oral formulation.

According to one aspect of the invention, the dosage form is a solid or semi-solid oral formulation.

It is further provided for a tablet comprising the pharmaceutical composition according to the invention.

The invention further relates to a process for preparing a pharmaceutical composition comprising a *tert*-butyl amine salt of a compound of formula (I) as well as free acid of the compound:



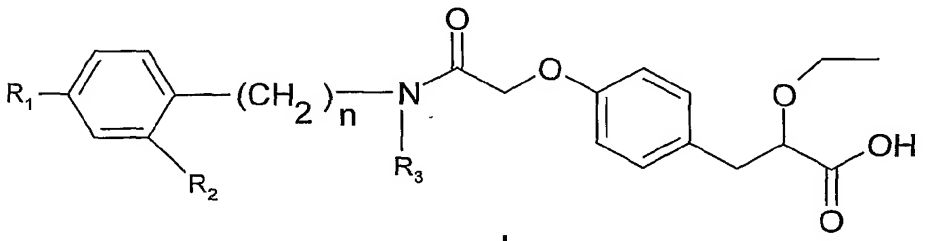
I

wherein n is 1 or 2, R^1 represents hydrogen, chloro, trifluoromethyl or trifluoromethoxy, R^2 represents hydrogen or fluoro and R^3 represents a C_{2-6}alkyl group,
comprising the steps of:

a) granulating a *tert*-butyl amine salt of a compound of formula (I);

b) drying the granules.

The invention further relates to a process for preparing tablets including a pharmaceutical composition comprising a *tert*-butyl amine salt of a compound of formula (I) as well as free acid of the compound:



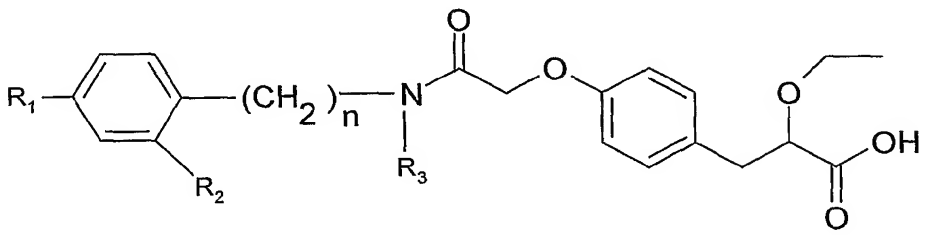
I

wherein n is 1 or 2, R^1 represents hydrogen, chloro, trifluoromethyl or trifluoromethoxy, R^2 represents hydrogen or fluoro and R^3 represents a C_{2-6}alkyl group,
comprising the steps of:

a) blending a tert-butyl amine salt of a compound of formula (I) with excipients;

b) compressing the blend into tablets.

The invention further relates to a process for preparing tablets including a pharmaceutical composition comprising a *tert*-butyl amine salt of a compound of formula (I) as well as free acid of the compound:



I

wherein n is 1 or 2, R^1 represents hydrogen, chloro, trifluoromethyl or trifluoromethoxy, R^2 represents hydrogen or fluoro and R^3 represents a C_{2-6}alkyl group, comprising the steps of:

a) preparing tablets comprising the salt;

b) coating the tablets.

The compounds comprised in the composition of the present invention have activity as medicaments. In particular the compounds are highly potent agonists of PPARα. In addition the compounds are also agonists of PPAR$_\gamma$. The term agonists as used herein, includes partial agonists. Their biological activity is described in WO 03/051821 and WO 2004/05602.

Methods of preparation of the *tert*-butyl amine salt

The *tert*-butyl amine salt of the invention was prepared by dissolving (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid in an inert solvent at a temperature in the range of 0-100°C and then adding the tert-butyl amine either neat or as a solution in an inert solvent and isolating the solid salt. The salt may be isolated by cooling the reaction solution and optionally seeding the solution with the desired product and/or concentrating the solution. Optionally the product may be isolated by adding an antisolvent to a solution of the product in an inert solvent. The solid may be collected by methods known to those skilled in the art for example filtration or centrifugation. This includes supercritical crystallisation with a solvent, e.g. acetone and/or ethanol, and an antisolvent, e.g. carbon dioxide.

In another aspect the present invention provides the compound obtainable by reacting (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid and *tert*-butylamine in an inert solvent, particularly acetone and isolating the product. Particularly, one equivalent or less than three equivalents of *tert*-butylamine is used.

As used herein, the term "C_2-C_6 alkyl" denotes a straight or branched alkyl group having from 2 to 6 carbons. Examples of said C_2-C_6 alkyl include ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl and straight- and branched-chained pentyl and hexyl. For parts of the range "C_2-C_6 alkyl", subranges thereof are contemplated such as C_2-C_5 alkyl, C_2-C_4 alkyl, C_4-C_5 alkyl, C_3-C_6 alkyl etc.

The expression "inert solvent" refers to a solvent that does not react with the starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

By "crystalline form" is meant a certain solid and/or liquid state modification. Such a crystalline form may either be amorphous or crystalline. Such a crystalline form may also appear in the form of a co-crystal, containing at least one other substance.

As used herein, the term "solvates" pertains to a compound having a number of solvent molecules incorporated in a crystalline form containing the molecule.

By "drying the granules" is meant a process that supplies energy to granules and allows evaporation of volatile substances.

Unless stated otherwise, any percentage is given by molar basis.

The present invention also encompasses prodrugs of compounds of the invention, i e second compounds which are converted to the first compounds in vivo.

In vivo cleavable esters are just one type of prodrug of the parent molecule. An *in vivo* hydrolysable (or cleavable) ester of a compound of the present invention that contains a carboxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid. Suitable pharmaceutically acceptable esters for carboxy include C_1-C_8 alkoxymethyl esters, for example, methoxymethyl, C_1-C_8 alkanoloxymethyl ester, for example, pivaloyloxymethyl; phthalidyl esters; C_3-C_8 cycloalkoxycarbonyloxy-C_1-C_8 alkyl esters, for example, 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters, for example, 5-methyl-1,3-dioxolen-2-onylmethyl; and C_1-C_8 alkoxycarbonyloxyethyl esters, for example, 1-methoxycarbonyloxymethyl; and may be formed at any carboxy group in the compounds of the present invention.

As used herein, the term "pharmaceutically acceptable salts" includes acid addition salts and base addition salts. Such salts may be formed by conventional means, for example by reaction of a free acid or a free base form of a compound of the invention with one or more equivalents of an appropriate acid or base, optionally in a solvent, or in a medium in which the salt is insoluble, followed by removal of said solvent, or said medium, using standard techniques (e.g. *in vacuo* or by freeze-drying). Salts may also be prepared by exchanging a counter-ion of a compound of the invention in the form of a salt with another counter-ion using a suitable ion exchange resin.

Suitable acids are non-toxic and include e g, but are not limited to, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulphuric acid, nitric acid, acetic acid, citric acid, asorbic acid, lactic acid, malic acid, and tartaric acid. Suitable bases are non-toxic and include e g, but are not limited to, sodium hydroxide, potassium hydroxide, ammonia, methylamine, dimethylamine, trimethylamine, tert-butylamine, and triethylamine.

Pharmaceutical preparations

The compounds of the invention will normally be administered via the oral, parenteral, intravenous, intramuscular, subcutaneous or in other injectable ways, buccal, rectal, vaginal, transdermal and/or nasal route and/or via inhalation, in the form of pharmaceutical preparations in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses.

Suitable daily doses of the compound of the invention in therapeutical treatment of humans are about 0.00001-100 mg/kg body weight, preferably 0.00001-10 mg/kg body weight.

Oral formulations are preferred particularly tablets or capsules which may be formulated by methods known to those skilled in the art to provide doses of the active compound in the range of 1 μg to 500mg, for example 5μg, 10μg, 0.1mg, 1 mg, 2.5 mg, 5 mg, 10 mg, 25mg, 50mg, 100mg and 250mg.

According to a further aspect of the invention there is thus provided a pharmaceutical formulation including the compound of the invention in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

Pharmacological properties

The compounds of the invention are useful for the prophylaxis and/or treatment of clinical conditions associated with inherent or induced reduced sensitivity to insulin (insulin resistance) and associated metabolic disorders (also known as metabolic syndrome). These clinical conditions will include, but will not be limited to, general obesity, abdominal obesity,

arterial hypertension, hyperinsulinaemia, hyperglycaemia, type 2 diabetes and the dyslipidaemia characteristically appearing with insulin resistance. This dyslipidaemia, also known as the atherogenic lipoprotein profile, is characterised by moderately elevated non-esterified fatty acids, elevated very low density lipoprotein (VLDL) triglyceride rich particles, high Apo B levels, low high density lipoprotein (HDL) levels associated with low apoAI particle levels and high Apo B levels in the presence of small, dense, low density lipoproteins (LDL) particles, phenotype B.

The compounds of the present invention are expected to be useful in treating patients with combined or mixed hyperlipidemias or various degrees of hypertriglyceridemias and postprandial dyslipidemia with or without other manifestations of the metabolic syndrome. Treatment with the present compounds is expected to lower the cardiovascular morbidity and mortality associated with atherosclerosis due to their antidyslipidaemic as well as antiinflammatory properties. The cardiovascular disease conditions include macro-angiopathies of various internal organs causing myocardial infarction, congestive heart failure, cerebrovascular disease and peripheral arterial insufficiency of the lower extremities. Because of its insulin sensitizing effect the compound is also expected to prevent or delay the development of type 2 diabetes from the metabolic syndrome and diabetes of pregnancy. Therefore the development of long-term complications associated with chronic hyperglycaemia in diabetes mellitus such as the micro-angiopathies causing renal disease, retinal damage and peripheral vascular disease of the lower limbs are expected to be delayed. Furthermore the compound may be useful in treatment of various conditions outside the cardiovascular system whether or not associated with insulin resistance, like polycystic ovarian syndrome, obesity, cancer and states of inflammatory disease including neurodegenerative disorders such as mild cognitive impairment, Alzheimer's disease, Parkinson's disease and multiple sclerosis.

The compounds of the present invention are expected to be useful in controlling glucose levels in patients suffering from type 2 diabetes.

The present invention provides a method of treating or preventing dyslipidemias, the insulin resistance syndrome and/or metabolic disorders (as defined above) comprising the

administration of a compound of the present invention to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating or preventing type 2 diabetes comprising the administration of an effective amount of a compound of the present invention to a mammal (particularly a human) in need thereof.

In a further aspect the present invention provides the use of a compound of the present invention as a medicament.

In a further aspect the present invention provides the use of a compound of the present invention in the manufacture of a medicament for the treatment of insulin resistance and/or metabolic disorders.

Combination Therapy

The compounds of the invention may be combined with another therapeutic agent that is useful in the treatment of disorders associated with the development and progress of atherosclerosis such as hypertension, hyperlipidaemias, dyslipidaemias, diabetes and obesity. The compound of the invention may be combined with another therapeutic agent that decreases the ratio of LDL:HDL or an agent that causes a decrease in circulating levels of LDL-cholesterol. In patients with diabetes mellitus the compound of the invention may also be combined with therapeutic agents used to treat complications related to micro-angiopathies.

A compound of the invention may be used alongside other therapies for the treatment of metabolic syndrome or type 2 diabetes and its associated complications, these include biguanide drugs, for example metformin, phenformin and buformin, insulin (synthetic insulin analogues, amylin) and oral antihyperglycemics (these are divided into prandial glucose regulators and alpha-glucosidase inhibitors). An example of an alpha-glucosidase inhibitor is acarbose or voglibose or miglitol. An example of a prandial glucose regulator is repaglinide or nateglinide.

In another aspect of the invention, the compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of salt or prodrug thereof, may be administered in association with a PPAR modulating agent. PPAR modulating agents include but are not limited to a PPAR alpha and/or gamma and/or delta agonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable PPAR alpha and/or gamma agonists, pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof are well known in the art. These include the compounds described in WO 01/12187, WO 01/12612, WO 99/62870, WO 99/62872, WO 99/62871, WO 98/57941, WO 01/40170, WO 04/000790, WO 04/000295, WO 04/000294, WO 03/051822, WO 03/051821, WO 02/096863, WO 03/051826, WO 02/085844, WO 01/040172, J Med Chem, 1996, 39, 665, Expert Opinion on Therapeutic Patents, 10 (5), 623-634 (in particular the compounds described in the patent applications listed on page 634) and J Med Chem, 2000, 43, 527 which are all incorporated herein by reference. Particularly a PPAR alpha and/or gamma and/or delta agonist refers to muraglitazar (BMS 298585), rivoglitazone (CS-011), netoglitazone (MCC-555), balaglitazone (DRF-2593, NN-2344), clofibrate, fenofibrate, bezafibrate, gemfibrozil, ciprofibrate, pioglitazone, rosiglitazone, AVE-0847, AVE-8134, CLX-0921, DRF-10945, DRF-4832, LY-518674, LY-818, LY-929, 641597, GW-590735, GW-677954, GW-501516, MBX-102, ONO-5129, KRP-101, R-483 (BM131258), TAK-559 or TAK-654. Particularly a PPAR alpha and/or gamma and/or delta agonist refers to tesaglitazar ((S)-2-ethoxy-3-[4-(2-{4-methanesulphonyl-oxyphenyl}ethoxy)phenyl]propanoic acid) and pharmaceutically acceptable salts thereof.

In addition a compound of the invention may be used in conjunction with a sulfonylurea for example: glimepiride, glibenclamide (glyburide), gliclazide, glipizide, gliquidone, chloropropamide, tolbutamide, acetohexamide, glycopyramide, carbutamide, glibonuride, glisoxepid, glybuthiazole, glibuzole, glyhexamide, glymidine, glypinamide, phenbutamide, tolcylamide and tolazamide. Preferably the sulfonylurea is glimepiride or glibenclamide (glyburide). More preferably the sulfonylurea is glimepiride. The present invention includes administration of a compound of the present invention in conjunction with one, two or more existing therapies described in this combination section. The doses of the other existing therapies for the treatment of type 2 diabetes and its associated complications will be those known in the art and approved for use by regulatory bodies for example the FDA and may be found in the Orange Book published by the FDA. Alternatively smaller doses may be used as

a result of the benefits derived from the combination. The present invention also includes a compound of the present invention in combination with a cholesterol-lowering agent. The cholesterol-lowering agents referred to in this application include but are not limited to inhibitors of HMG-CoA reductase (3-hydroxy-3-methylglutaryl coenzyme A reductase). Suitably the HMG-CoA reductase inhibitor is a statin selected from the group consisting of atorvastatin, bervastatin, cerivastatin, dalvastatin, fluvastatin, itavastatin, lovastatin, mevastatin, nicostatin, nivastatin, pravastatin and simvastatin, or a pharmaceutically acceptable salt, especially sodium or calcium, or a solvate thereof, or a solvate of such a salt. A particular statin is atorvastatin, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof. A more particular statin is atorvastatin calcium salt. A particularly preferred statin is, however, a compound with the chemical name (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)-amino]-pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid, [also known as (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[*N*-methyl-*N*-(methylsulfonyl)-amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt. The compound (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl-(methylsulfonyl)-amino]-pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid, and its calcium and sodium salts are disclosed in European Patent Application, Publication No. EP-A-0521471, and in Bioorganic and Medicinal Chemistry, (1997), 5(2), 437-444. This latter statin is now known under its generic name rosuvastatin.

In the present application, the term "cholesterol-lowering agent" also includes chemical modifications of the HMG-CoA reductase inhibitors, such as esters, prodrugs and metabolites, whether active or inactive.

The present invention also includes a compound of the present invention in combination with a bile acid sequestering agent, for example colestipol or cholestyramine or cholestagel.

The present invention also includes a compound of the present invention in combination with an inhibitor of the ileal bile acid transport system (IBAT inhibitor).

Suitable compounds possessing IBAT inhibitory activity have been described, see for instance the compounds described in WO 93/16055, WO 94/18183, WO 94/18184, WO 96/05188,

WO 96/08484, WO 96/16051, WO 97/33882, WO 98/07449, WO 98/03818, WO 98/38182, WO 99/32478, WO 99/35135, WO 98/40375, WO 99/35153, WO 99/64409, WO 99/64410, WO 00/01687, WO 00/47568, WO 00/61568, WO 00/62810, WO 01/68906, DE 19825804, WO 00/38725, WO 00/38726, WO 00/38727, WO 00/38728, WO 00/38729, WO 01/68906, WO 01/66533, WO 02/32428, WO 02/50051, EP 864 582, EP 489 423, EP 549 967, EP 573 848, EP 624 593, EP 624 594, EP 624 595 and EP 624 596 and the contents of these patent applications are incorporated herein by reference. Further suitable compunds possessing IBAT inhibitory activity have been described in WO 94/24087, WO 98/56757, WO 00/20392, WO 00/20393, WO 00/20410, WO 00/20437, WO 01/34570, WO 00/35889, WO 01/68637, WO 02/08211, WO 03/020710, WO 03/022825, WO 03/022830, WO 03/022286, WO 03/091232, WO 03/106482, JP 10072371, US 5070103, EP 251 315, EP 417 725, EP 869 121, EP 1 070 703 and EP 597 107 and the contents of these patent applications are incorporated herein by reference.

Particular classes of IBAT inhibitors suitable for use in the present invention are benzothiepines, and the compounds described in the claims, particularly claim 1, of WO 00/01687, WO 96/08484 and WO 97/33882 are incorporated herein by reference. Other suitable classes of IBAT inhibitors are the 1,2-benzothiazepines, 1,4-benzothiazepines and 1,5-benzothiazepines. A further suitable class of IBAT inhibitors is the 1,2,5-benzothiadiazepines.

One particular suitable compound possessing IBAT inhibitory activity is (3*R*,5*R*)-3-butyl-3-ethyl-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,4-benzothiazepin-8-yl-ß-D-glucopyranosiduronic acid (EP 864 582). Other suitable IBAT inhibitors include one of:

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N'*-(carboxymethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(carboxymethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N'*-(2-sulphoethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N'*-(2-sulphoethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-sulphoethyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-carboxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(5-carboxypentyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{α-[*N'*-(2-sulphoethyl)carbamoyl]-2-fluorobenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(R)-(2-hydroxy-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(R)-(2-hydroxy-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{*N*-[(R)-α-(*N'*-{(R)-1-[*N''*-(R)-(2-hydroxy-1-carboxyethyl)carbamoyl]-2-hydroxyethyl}carbamoyl)benzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{α-[*N'*-(carboxymethyl)carbamoyl]-benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{α-[*N'*-((ethoxy)(methyl)phosphoryl-methyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-{*N*-[(R)-α-(*N'*-{2-[(hydroxy)(methyl)-phosphoryl]ethyl}carbamoyl)benzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-methylthio-1-carboxyethyl)-carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{*N*-[(R)-α-(*N'*-{2-[(methyl)(ethyl)-phosphoryl]ethyl}carbamoyl)-4-hydroxybenzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{*N*-[(R)-α-(*N'*-{2-[(methyl)(hydroxy)-phosphoryl]ethyl}carbamoyl)-4-hydroxybenzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[(R)-*N'*-(2-methylsulphinyl-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methoxy-8-[*N*-{(R)-α-[*N'*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((R)-1-carboxy-2-methylthio-ethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxybutyl)-carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxypropyl)-carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxyethyl)-carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxyethyl)-carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((R)-1-carboxy-2-methylthioethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-{(S)-1-[*N*-((S)-2-hydroxy-1-carboxyethyl)carbamoyl]propyl}carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxypropyl)-carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-((R/S)-α-{*N*-[1-(R)-2-(S)-1-hydroxy-1-(3,4-dihydroxyphenyl)prop-2-yl]carbamoyl}-4-hydroxybenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; and

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to an additional further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the present invention optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration one or more of the following agents selected from:

a CETP (cholesteryl ester transfer protein) inhibitor, for example those referenced and described in WO 00/38725 page 7 line 22 - page 10, line 17 which are incorporated herein by reference;

a cholesterol absorption antagonist for example azetidinones such as SCH 58235 and those described in US 5,767,115 which are incorporated herein by reference;

a MTP (microsomal transfer protein) inhibitor for example those described in Science, 282, 751-54, 1998 which are incorporated herein by reference;

a nicotinic acid derivative, including slow release and combination products, for example, nicotinic acid (niacin), acipimox and niceritrol;

a phytosterol compound for example stanols;

probucol;

an omega-3 fatty acid for example Omacor™;

an anti-obesity compound for example orlistat (EP 129,748) and sibutramine (GB 2,184,122 and US 4,929,629);

an antihypertensive compound for example an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, an andrenergic blocker, an alpha andrenergic blocker, a beta andrenergic blocker for example metoprolol, a mixed alpha/beta andrenergic blocker, an andrenergic stimulant, calcium channel blocker, an AT-1 blocker, a saluretic, a diuretic or a vasodilator;

a CB1 antagonist or inverse agonist for example as described in WO01/70700 and EP 65635 ;

aspirin;

a Melanin concentrating hormone (MCH) antagonist;

a PDK inhibitor; or

modulators of nuclear receptors for example LXR, FXR, RXR, and RORalpha;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Particular ACE inhibitors or pharmaceutically acceptable salts, solvates, solvate of such salts or prodrugs thereof, including active metabolites, which can be used in combination with a compound of the invention include but are not limited to, the following compounds: alacepril, alatriopril, altiopril calcium, ancovenin, benazepril, benazepril hydrochloride, benazeprilat, benzoylcaptopril, captopril, captopril-cysteine, captopril-glutathione, ceranapril, ceranopril,

ceronapril, cilazapril, cilazaprilat, delapril, delapril-diacid, enalapril, enalaprilat, enapril, epicaptopril, foroxymithine, fosfenopril, fosenopril, fosenopril sodium, fosinopril, fosinopril sodium, fosinoprilat, fosinoprilic acid, glycopril, hemorphin-4, idrapril, imidapril, indolapril, indolaprilat, libenzapril, lisinopril, lyciumin A, lyciumin B, mixanpril, moexipril, moexiprilat, moveltipril, muracein A, muracein B, muracein C, pentopril, perindopril, perindoprilat, pivalopril, pivopril, quinapril, quinapril hydrochloride, quinaprilat, ramipril, ramiprilat, spirapril, spirapril hydrochloride, spiraprilat, spiropril, spiropril hydrochloride, temocapril, temocapril hydrochloride, teprotide, trandolapril, trandolaprilat, utibapril, zabicipril, zabiciprilat, zofenopril and zofenoprilat. Preferred ACE inhibitors for use in the present invention are ramipril, ramiprilat, lisinopril, enalapril and enalaprilat. More preferred ACE inhibitors for uses in the present invention are ramipril and ramiprilat.
Preferred angiotensin II antagonists, pharmaceutically acceptable salts, solvates, solvate of such salts or prodrugs thereof for use in combination with a compound of the invention include, but are not limited to, compounds: candesartan, candesartan cilexetil, losartan, valsartan, irbesartan, tasosartan, telmisartan and eprosartan. Particularly preferred angiotensin II antagonists or pharmaceutically acceptable derivatives thereof for use in the present invention are candesartan and candesartan cilexetil.

Therefore, in an additional feature of the invention, there is provided a method for for the treatment of type 2 diabetes and its associated complications in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of the present invention in simultaneous, sequential or separate administration with an effective amount of at least one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore, in an additional feature of the invention, there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of the present invention of a compound of the invention in simultaneous, sequential or separate administration with an effective amount of at least one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the present invention and at least one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the present invention there is provided a kit comprising a compound of the present invention and at least one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the present invention there is provided a kit comprising:
a) a compound of the present invention in a first unit dosage form;
b) at least one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; in a second unit dosage form; and
c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:
a) a compound of the present invention together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;
b) at least one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and
c) container means for containing said first and second dosage forms.

According to another feature of the invention there is provided the use of a compound of the present invention of the present invention and at least one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the the treatment of metabolic syndrome or type 2 diabetes and its associated complications in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the present invention and at least one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the present invention optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of at least one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Experimental

^{1}H NMR and ^{13}C NMR measurements were performed on a Varian Mercury 300 or Varian UNITY plus 400, 500 or 600 spectrometers, operating at ^{1}H frequencies of 300, 400, 500 and 600 MHz, respectively, and at ^{13}C frequencies of 75, 100, 125 and 150 MHz, respectively. Measurements were made on the delta scale (δ).

Unless otherwise stated, chemical shifts are given in ppm with the solvent as internal standard.

X-ray powder diffraction analysis (XRPD) was performed using variable slits on samples prepared according to standard methods with or without using an internal standard. Standard methods are, for example described in Giacovazzo, C. *et al* (1995), *Fundamentals of Crystallography*, Oxford University Press; Jenkins, R. and Snyder, R. L. (1996), *Introduction to X-Ray Powder Diffractometry*, John Wiley & Sons, New York; Bunn, C. W. (1948), *Chemical Crystallography*, Clarendon Press, London; or Klug, H. P. & Alexander, L. E. (1974), *X-ray Diffraction Procedures*, John Wiley and Sons, New York. X-ray analyses were

performed using Cu-radiation on a Siemens D5000 diffractometer or a Philips X'Pert MPD. The X-axis in the figures below is 2-theta and the Y axis is intensity.

Differential scanning calorimetry (DSC) was performed using a Mettler DSC820, a Mettler DSC820E or a Perkin Elmer DSC 7 instrument, according to standard methods, for example those described in Höhne, G. W. H. *et al* (1996), *Differential Scanning Calorimetry*, Springer, Berlin.

Thermogravimetric analysis (TGA) was performed using a Mettler Toledo TGA850, a Mettler Toledo TG851 or a Perkin Elmer TGA 7 instrument.

It will be appreciated by the skilled person that crystalline forms of compounds of the invention may be prepared by analogy with processes described herein and/or in accordance with the Examples below, and may show essentially the same XRPD diffraction patterns and/or DSC and/or TGA thermograms as those disclosed herein. By "essentially the same" XRPD diffraction patterns and/or DSC and/or TGA thermograms, we include those instances when it is clear from the relevant patterns and/or thermograms (allowing for experimental error) that essentially the same crystalline form has been formed. When provided, DSC onset temperatures may vary in the range ±5°C (e.g. ±2°C), and XRPD distance values may vary in the range ±2 on the last decimal place. It will be appreciated by the skilled person that XRPD intensities may vary when measured for essentially the same crystalline form for a variety of reasons including, for example, preferred orientation.

Abbreviations

NMR Abbreviations

NMR	Nuclear Magnetic Resonance
t	triplet
s	singlet
d	doublet
q	quartet
m	multiplet
bs	broad singlet

XRPD Abbreviations

XRPD	X-ray powder diffraction
d-value	the spacing between successive parallel *hkl* planes in a crystal lattice

Intensity (rel %)	Definition
25 - 100	vs (very strong)
10 - 25	s (strong)
3 - 10	m (medium)
1 - 3	w (weak)

TGA	thermogravimetric analysis
DSC	differential scanning calorimetry

Examples

Example 1

(2*S*)-2-Ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid

(i) Ethyl (2*S*)-3-{4-[2-(benzyloxy)-2-oxoethoxy]phenyl}-2-ethoxypropanoate

To a solution of ethyl (2*S*)-2-ethoxy-3-(4-hydroxyphenyl)propanoate (23.8 g, 100 mmol, prepared as described in WO99/62872) in acetonitrile (200 mL) was added anhydrous potassium carbonate (31.9 g, 231 mmol) followed by benzyl bromoacetate (17.4 mL, 110 mmol) and the reaction mixture was refluxed overnight. The reaction mixture was allowed to cool to room temperature, insoluble salts were filtered off and the solution was concentrated *in vacuo*. The residue was taken up in ethyl acetate (300 mL), and the organic phase was washed with aqueous $NaHCO_3$ (3 x 100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification on silica gel with methylene chloride as the eluent and collection of pure fractions yielded 22.4 g (58%) of a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.16 (t, 3H), 1.22 (t, 3H), 2.93–2.97 (m, 2H), 3.35 (m, 1H), 3.60 (m, 1H), 3.97 (m, 1H), 4.16 (q, 2H), 4.64 (s, 2H), 5.23 (s, 2H), 6.82 (d, 2H), 7.15 (d, 2H), 7.32–7.39 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 15.2, 38.6, 60.9, 65.6, 66.3, 67.0, 80.4, 114.6, 128.5, 128.6, 128.7, 130.6, 135.3, 156.7, 169.0, 172.6.

(ii) {4-[(2*S*)-2,3-Diethoxy-3-oxopropyl]phenoxy}acetic acid

To a solution of ethyl (2*S*)-3-{4-[2-(benzyloxy)-2-oxoethoxy]phenyl}-2-ethoxypropanoate (22.33 g, 57.8 mmol) in freshly distilled THF (290 mL) was added Pd/C (10%, 3.1 g) and the reaction mixture was hydrogenated under atmospheric pressure at room temperature overnight. The mixture was filtered through a plug of Celite and the filtrate was concentrated *in vacuo* to afford 16.6 g (97%) of a light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (t, 3H), 1.21 (t, 3H), 2.93–2.98 (m, 2H), 3.35 (m, 1H), 3.60 (m, 1H), 3.97 (m, 1H), 4.16 (q, 2H), 4.65 (s, 2H), 6.84 (d, 2H), 7.17 (d, 2H), 8.48 (bs, 1H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 15.1, 38.5, 61.0, 65.1, 66.4, 80.3, 114.6, 130.7, 130.9, 156.4, 172.7, 173.7

(iii) Ethyl (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)-propanoate

To a solution of {4-[(2*S*)-2,3-diethoxy-3-oxopropyl]phenoxy}acetic acid (0.110 g, 0.37 mmol) in methylene chloride (3.7 mL) were added N-hexyl-2-phenylethylamine (0.080 g, 0.39 mmol) and DMAP (0.045 g, 0.37 mmol) followed by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.071 g, 0.37 mmol), and the reaction mixture was stirred at room temperature overnight. The mixture was diluted with methylene chloride (25 mL), and the organic phase was washed with 5% HCl (3 x 25 mL), aqueous $NaHCO_3$ (25 mL) and brine (25 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification on a prepacked column of silica gel (Isolute® SPE Column, 5 g Si/25 mL) with methanol (0–1% gradient) in methylene chloride as the eluent yielded 0.125 g (70%) of a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82–0.92 (m, 3H), 1.16 (t, 3H), 1.19–1.33 (m, 9H), 1.45–1.65 (m, 2H), 2.82-2.90 (m, 2H), 2.91–2.98 (m, 2H), 3.12–3.21 and 3.29–3.42 (2m, 3H, rotamers) 3.50–3.65 (m, 3H), 3.95 (m,1H), 4.16 (q, 2H), 4.39 and 4.65 (2s, 2H, rotamers), 6.75 and 6.86 (2d, 2H, rotamers), 7.10–7.34 (m, 7H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 14.1, 14.3, 15.1, 22.6, 26.5, 26.7, 27.4, 29.0, 31.5, 31.6, 33.9, 35.3, 38.5, 45.9, 48.1, 48.3, 48.9, 60.8, 66.2, 67.5, 80.4, 114.5, 126.4, 126.9, 128.5, 128.9, 130.1, 130.2, 130.5, 130.5, 138.3, 139.2, 156.9, 157.0, 167.6, 167.8, 172.5. (The number of peaks is larger than the number of carbon atoms due to rotamers.)

(iv) (2*S*)-2-Ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid

To a solution of ethyl (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoate (0.081 g, 0.17 mmol) in THF (8.6 mL) was added 4.3 mL of a 0.10 M LiOH solution and the reaction mixture was stirred at room temperature overnight. The reaction mixture was acidified with 2M HCl and extracted with ethyl acetate (3 x 25mL). The combined organic phase was washed with brine (25 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford 0.073 g (96%) of a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82–0.93 (m, 3H), 1.15 (t, 3H), 1.20–1.35 (m, 6H), 1.47–1.62 (m, 2H), 2.80–2.99 (m, 3H), 3.00–3.09 (m, 1H), 3.11–3.21 and 3.31–3.44 (2m, 3H, rotamers), 3.50–3.67 (m, 3H), 4.01 (m, 1H), 4.40 and 4.66 (2s, 2H, rotamers), 6.75 and 6.85 (2d, 2H, rotamers), 7.10–7.35 (m, 7H), 8.86 (bs, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 14.1, 15.1, 22.6, 22.6, 26.6, 26.7, 27.3, 28.9, 31.5, 31.6, 33.8, 35.2, 38.1, 46.1, 48.3, 48.4, 49.0, 66.7, 67.4, 79.9, 114.6, 126.4, 127.0, 128.6, 128.9, 130.0, 130.1, 130.6, 130.7, 138.2, 139.1, 156.9, 157.0, 168.1, 168.2, 175.6. (The number of peaks is larger than the number of carbon atoms due to rotamers.)

Example 2

(2*S*)-3-(4-{2-[Benzyl(hexyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

(i) Ethyl (2*S*)-3-{4-[2-(benzyloxy)-2-oxoethoxy]phenyl}-2-ethoxypropanoate

See under Example 1, step (i)

(ii) {4-[(2*S*)-2,3-Diethoxy-3-oxopropyl]phenoxy}acetic acid

See under Example 1, step (ii)

(iii) Ethyl (2*S*)-3-(4-{2-[benzyl(hexyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoate

To a solution of {4-[(2*S*)-2,3-diethoxy-3-oxopropyl]phenoxy}acetic acid (0.110 g, 0.37 mmol) in methylene chloride (3.7 mL) were added N-hexyl-benzylamine (0.079 g, 0.41 mmol) and DMAP (0.045 g, 0.37 mmol) followed by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.071 g, 0.37 mmol) and the reaction mixture was stirred at room temperature overnight. The mixture was diluted with methylene chloride (25 mL), and the organic phase was washed with 5% HCl (3 x 25 mL), aqueous $NaHCO_3$ (25 mL), and brine (25 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification on a prepacked column of silica gel (Isolute® SPE Column, 5 g Si/25 mL) with methanol (0–1% gradient) in methylene chloride as the eluent yielded 0.139 g (80%) of a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.81–0.90 (m, 3H), 1.11–1.32 (m, 12H), 1.46–1.62 (m, 2H), 2.88–3.00 (m, 2H), 3.21–3.29 and 3.29–3.40 (2m, 3H, rotamers), 3.59 (m, 1H), 3.95 (m, 1H), 4.10–4.19 (m, 2H), 4.60 and 4.61 (2s, 2H, rotamers), 4.65 and 4.73 (2s, 2H, rotamers), 6.77 and 6.87 (2d, 2H, rotamers), 7.07–7.37 (m, 7H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 14.2, 15.1, 22.5, 26.5, 27.1, 28.4, 31.4, 31.5, 38.4, 46.3, 46.5, 48.2, 50.5, 60.7, 66.1, 67.5, 67.8, 80.3, 114.4, 114.5, 126.6, 127.3, 127.6, 128.0, 128.5, 128.8, 130.2, 130.2, 130.4, 130.5, 136.6, 137.2, 156.8, 156.9, 168.0, 168.1, 172.4. (The number of peaks is larger than the number of carbon atoms due to rotamers.)

(iv) (2*S*)-3-(4-{2-[Benzyl(hexyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

To a solution of ethyl (2*S*)-3-(4-{2-[benzyl(hexyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoate (0.080 g, 0.17 mmol) in THF (8.6 mL) was added 4.3 mL of a 0.10 M LiOH solution and the reaction mixture was stirred at room temperature overnight. The reaction mixture was acidified with 2M HCl and extracted with ethyl acetate (3 x 25mL). The combined organic phase was washed with brine (25 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford 0.068 g (90%) of a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.80–0.92 (m, 3H), 1.11–1.18 (m, 3H), 1.18–1.33 (m, 6H), 1.46–1.63 (m, 2H), 2.87–3.11 (m, 2H), 3.20–3.30 and 3.32–3.45 (2m, 3H, rotamers), 3.61 (m, 1H), 4.01 (m, 1H), 4.61 and 4.63 (2s, 2H, rotamers), 4.67 and 4.75 (2s, 2H, rotamers), 6.77 and 6.88 (2d, 2H, rotamers), 7.10–7.40 (m, 7H), 8.79 (bs, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 15.1, 22.6, 26.6, 27.1, 28.4, 31.5, 31.5, 31.6, 38.1, 46.5, 46.6, 48.5, 50.7, 66.7, 67.4, 67.7, 79.9, 114.6, 114.7, 126.7, 127.5, 127.8, 128.2, 128.7, 129.0, 130.1, 130.1, 130.6, 130.7, 136.5, 137.0, 156.9, 157.0, 168.5, 168.6, 175.6. (The number of peaks is larger than the number of carbon atoms due to rotamers.)

Example 3

(2*S*)-3-[4-(2-{Butyl[2-fluoro-4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]-2-ethoxypropanoic acid

(i) Ethyl (2*S*)-3-{4-[2-(benzyloxy)-2-oxoethoxy]phenyl}-2-ethoxypropanoate

To a solution of ethyl (2*S*)-2-ethoxy-3-(4-hydroxyphenyl)propanoate (23.8 g, 100 mmol, prepared as described in WO99/62872) in acetonitrile (200 mL) was added anhydrous potassium carbonate (31.9 g, 231 mmol) followed by benzyl bromoacetate (17.4 mL, 110 mmol) and the reaction mixture was refluxed overnight. The reaction mixture was allowed to cool to room temperature, insoluble salts were filtered off and the solution was concentrated *in vacuo*. The residue was taken up in ethyl acetate (300 mL), and the organic phase was washed with aqueous

$NaHCO_3$ (3 x 100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification on silica gel with methylene chloride as the eluent and collection of pure fractions yielded 22.4 g (58%) of a yellow oil.

^1H NMR (400 MHz, $CDCl_3$): δ 1.16 (t, 3H), 1.22 (t, 3H), 2.93–2.97 (m, 2H), 3.35 (m, 1H), 3.60 (m, 1H), 3.97 (m, 1H), 4.16 (q, 2H), 4.64 (s, 2H), 5.23 (s, 2H), 6.82 (d, 2H), 7.15 (d, 2H), 7.32–7.39 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 15.2, 38.6, 60.9, 65.6, 66.3, 67.0, 80.4, 114.6, 128.5, 128.6, 128.7, 130.6, 135.3, 156.7, 169.0, 172.6.

(ii) {4-[(2*S*)-2,3-Diethoxy-3-oxopropyl]phenoxy}acetic acid

To a solution of ethyl (2*S*)-3-{4-[2-(benzyloxy)-2-oxoethoxy]phenyl}-2-ethoxypropanoate (22.33 g, 57.8 mmol) in freshly distilled THF (290 mL) was added Pd/C (10%, 3.1 g) and the reaction mixture was hydrogenated under atmospheric pressure at room temperature overnight. The mixture was filtered through a plug of Celite and the filtrate was concentrated *in vacuo* to afford 16.6 g (97%) of a light yellow oil.

^1H NMR (400 MHz, $CDCl_3$): δ 1.15 (t, 3H), 1.21 (t, 3H), 2.93–2.98 (m, 2H), 3.35 (m, 1H), 3.60 (m, 1H), 3.97 (m, 1H), 4.16 (q, 2H), 4.65 (s, 2H), 6.84 (d, 2H), 7.17 (d, 2H), 8.48 (bs, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 15.1, 38.5, 61.0, 65.1, 66.4, 80.3, 114.6, 130.7, 130.9, 156.4, 172.7, 173.7.

(iii) *N*-Butyl-*N*-[2-fluoro-4-(trifluoromethyl)benzyl]amine

To a solution of 2-fluoro-4-(trifluoromethyl)benzaldehyde (3.84 g, 20.0 mmol) and *n*-butylamine (1.46 g, 20.0 mmol) in methanol (100 mL) were added acetic acid (4.6 mL, 80 mmol) and sodium cyanoborohydride (1.51 g, 24.0 mmol) and the solution was stirred at room temperature for 3 days. Water (10 mL) was added and the mixture was concentrated *in vacuo*. The residue was taken up in aqueous 1 M KOH (125 mL) and ethyl acetate (100 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (2 x 100 mL) and the combined

organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. Purification on a prepacked column of silica gel (Isolute® SPE Column, 70 g/150 mL) with ethyl acetate (33–100% gradient) in heptane as the eluent and collection of pure fractions yielded 1.28 g (26%) of a colourless oil of low viscosity.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (t, 3H), 1.28–1.41 (m, 2H), 1.44–1.55 (m, 2H), 2.62 (t, 2H), 3.88 (s, 2H), 7.29 (m, 1H), 7.38 (m, 1H), 7.51 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 20.6, 32.4, 47.0, 49.3, 112.8 (m), 121.1 (m), 123.5 (q), 130.5–131.6 (m), 130.8 (m), 132.0 (d), 160.8 (d).

(iv) Ethyl (2*S*)-3-[4-(2-{butyl[2-fluoro-4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy) phenyl]-2-ethoxypropanoate

To a solution of *N*-butyl-*N*-[2-fluoro-4-(trifluoromethyl)benzyl]amine (0.598 g, 2.40 mmol) and {4-[(2*S*)-2,3-diethoxy-3-oxopropyl]phenoxy}acetic acid (0.593 g, 2.00 mmol) in methylene chloride (20 mL) were added *N*,*N*-diisopropylethylamine (0.80 mL, 4.6 mmol) and *O*-(benzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium tetrafluoroborate (0.674 g, 2.10 mmol) and the reaction mixture was stirred at room temperature overnight. The resulting solution was diluted with methylene chloride (100 mL) and the organic phase was washed with 2 M HCl (3 x 75 mL), saturated aqueous $NaHCO_3$ (2 x 75 mL), and brine (75 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification on a prepacked column of silica gel (Isolute® SPE Column, 20 g/70 mL) with methanol (0–2% gradient) in methylene chloride as the eluent yielded 0.785 g (74%) of a pale yellowish-white oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84–0.97 (m, 3H), 1.11–1.19 (m, 3H), 1.19–1.40 (m, 5H), 1.45–1.65 (m, 2H), 2.90–2.99 (m, 2H), 3.29–3.40 (m, 3H), 3.60 (m, 1H), 3.96 (m, 1H), 4.16 (q, 2H), 4.68 (s, 2H), 4.72 and 4.74 (2s, 2H, rotamers), 6.70 and 6.86 (2d, 2H, rotamers), 7.10 and 7.17 (2d, 2H, rotamers), 7.21–7.40 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 14.3, 15.2, 20.2, 29.2, 30.9, 38.5, 42.1 (d), 44.6 (d), 46.2, 47.5, 60.9, 66.3, 67.6, 68.3, 80.4, 113.0 (m), 114.3, 114.6, 121.4 (m), 123.3 (q), 128.5 (m), 129.1

(d), 130.6, 130.6, 130.7, 131.0 (d), 131.0–132.2 (m), 156.6, 156.8, 160.3 (d), 160.5 (d), 168.5, 168.6, 172.6. (The number of peaks is larger than the number of carbon atoms due to rotamers.)

(v) (2*S*)-3-[4-(2-{Butyl[2-fluoro-4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]-2-ethoxypropanoic acid

To a solution of ethyl (2*S*)-3-[4-(2-{butyl[2-fluoro-4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]-2-ethoxypropanoate (0.748 g, 1.42 mmol) in acetonitrile (70 mL) was added aqueous 0.10 M LiOH (35 mL) and the reaction mixture was stirred at room temperature overnight. After neutralisation with 5% HCl, the solvent volume was reduced *in vacuo* and the remaining aqueous phase was acidified with 5% HCl and extracted with ethyl acetate (3 x 100 mL). The combined organic phase was washed with brine (100 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford 0.688 g (97%) of a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84–0.96 (m, 3H), 1.16 (t, 3H), 1.21–1.40 (m, 2H), 1.45–1.66 (m, 2H), 2.88–3.11 (m, 2H), 3.29–3.46 (m, 3H), 3.61 (m, 1H), 4.02 (m, 1H), 4.69 (s, 2H), 4.73 and 4.75 (2s, 2H, rotamers), 6.70 an 6.86 (2d, 2H, rotamers), 7.12 and 7.18 (2d, 2H, rotamers), 7.22–7.41 (m, 3H), 8.66 (bs, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 15.1, 20.1, 29.2, 30.8, 38.0, 42.2 (d), 44.6 (d), 46.3, 47.5, 66.8, 67.4, 68.1, 79.8, 113.0 (m), 114.4, 114.6, 121.4 (m), 123.3 (q), 128.3 (m), 129.1 (d), 130.2, 130.7, 130.8, 131.0 (d), 131.0–132.2 (m), 156.7, 156.9, 160.3 (d), 160.5 (d), 168.8, 168.9, 175.6. (The number of peaks is larger than the number of carbon atoms due to rotamers.)

Example 4

(2*S*)-3-(4-{2-[(4-Chlorobenzyl)(ethyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

(i) Ethyl (2*S*)-3-(4-{2-[(4-chlorobenzyl)(ethyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoate

To a solution of *N*-(4-chlorobenzyl)-*N*-ethylamine (0.150 g, 0.88 mmol) and {4-[(2*S*)-2,3-diethoxy-3-oxopropyl]phenoxy}acetic acid (0.270 g, 0.91 mmol) in methylene chloride (10 mL) were added *N*,*N*-diisopropylethylamine (0.34 mL, 1.9 mmol) and *O*-(benzotriazol-1-yl)-

N,N,N',N'-tetramethyluronium tetrafluoroborate (0.320 g, 1.00 mmol) and the reaction mixture was stirred at room temperature overnight. The resulting solution was diluted with methylene chloride (40 mL) and the organic phase was washed with 5% HCl (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification on a prepacked column of silica gel (Isolute® SPE Column, 50 g/150 mL) with methylene chloride/ethyl acetate 10:1 as the eluent yielded 0.24 g (61%) of a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.05–1.24 (m, 9H), 2.88–3.00 (m, 2H), 3.28–3.42 (m, 3H), 3.60 (m, 1H), 3.96 (m, 1H), 4.12–4.20 (m, 2H), 4.56 and 4.58 (2s, 2H, rotamers), 4.64 and 4.73 (2s, 2H, rotamers), 6.75 and 6.88 (2d, 2H, rotamers), 7.09–7.20 (m, 4H), 7.24 and 7.30 (2d, 2H, rotamers).

(ii) (2*S*)-3-(4-{2-[(4-Chlorobenzyl)(ethyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid

To a solution of ethyl (2*S*)-3-(4-{2-[(4-chlorobenzyl)(ethyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoate (0.240 g, 0.54 mmol) in THF (30 mL) was added aqueous 0.10 M LiOH (15 mL) and the solution was stirred at room temperature overnight. After neutralisation with 5% HCl, the solvent volume was reduced *in vacuo* and the remaining aqueous phase was acidified with 5% HCl and extracted with methylene chloride (2 x 50 mL). The combined organic phase was washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification on a prepacked column of silica gel (Isolute® SPE Column, 2 g/15 mL) with ethyl acetate as the eluent afforded 0.138 g (61%) of a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.05–1.21 (m, 6H), 2.94 (m, 1H), 3.04 (m, 1H), 3.30–3.45 (m, 3H), 3.61 (m, 1H), 4.01 (m, 1H), 4.57 and 4.58 (2s, 2H, rotamers), 4.66 and 4.73 (2s, 2H, rotamers), 6.74 and 6.87 (2d, 2H, rotamers), 7.10–7.20 (m, 4H), 7.24 and 7.30 (d, 2H), 7.98 (bs, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 12.3, 13.9, 15.1, 38.0, 41.2, 41.5, 47.6, 49.8, 66.7, 67.4, 68.0, 79.8, 114.5, 114.6, 128.3, 128.8, 129.1, 129.5, 130.2, 130.7, 133.3, 133.6, 135.0, 135.7, 156.7, 156.9, 168.4, 168.4, 175.5. (The number of peaks is larger than the number of carbon atoms due to rotamers.)

Example 5

(2*S*)-2-Ethoxy-3-[4-(2-{ethyl[4-(trifluoromethoxy)benzyl]amino}-2-oxoethoxy)phenyl]-propanoic acid

(i) *N*-[4-(Trifluoromethoxy)benzyl]acetamide

To a solution of 4-(trifluoromethoxy)benzylamine (3.46 g, 57.6 mmol) in DMF (75 mL) and acetic acid (10.0 g, 52.3 mmol) at –10 °C were added *O*-(benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate (20.2 g, 62.8 mmol) and *N*,*N*-diisopropylethylamine (20.0 mL, 115 mmol) and the reaction mixture was stirred at room temperature overnight. Ethyl acetate (200 mL) was added and the organic phase was washed with water (100 mL), 0.25 M NaOH (100 mL), saturated aqueous $NaHCO_3$ (100 mL), water (100 mL), 0.5 M HCl (100 mL), and water (100 mL), dried over $MgSO_4$, and concentrated *in vacuo* to afford 11.2 g (92%) of a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 2.03 (s, 3H), 4.43 (d, 2H), 5.83 (bs, 1H), 7.17 (d, 2H), 7.31 (d, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 22.9, 42.8, 120.5 (q), 121.1, 129.0, 137.3, 148.4, 170.6.

(ii) *N*-ethyl-*N*-[4-(Trifluoromethoxy)benzyl]amine

N-[4-(Trifluoromethoxy)benzyl]acetamide (10.4 g, 44.6 mmol) was dissolved in THF (100 mL) and cooled to –10 °C. Borane (56 mL of a 2 M solution of the dimethylsulfide complex in diethyl ether) was added and the reaction mixture was stirrred at –10 °C for 15 minuters and was then allowed to warm to room temperature. The reaction mixture was refluxed overnight and was then allowed to cool to room temperature. The reaction was quenched by careful addition of 10% HCl (30 mL) at 0 °C and the mixture was stirred at room temperature overnight and then concentrated *in vacuo*. The residue was taken up in water (200 mL) and diethyl ether (200 mL) and the phases were separated. Concentration *in vacuo* of the diethyl ether phase afforded 1.9 g (21 %) of the title compound as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (t, 3H), 2.72 (q, 2H), 3.83 (s, 2H), 3.86 (bs, 1H), 7.18 (d, 2H), 7.40 (d, 2H).

(iii) Ethyl (2*S*)-2-ethoxy-3-[4-(2-{ethyl[4-(trifluoromethoxy)benzyl]amino}-2-oxoethoxy)phenyl]propanoate

To a solution of *N*-ethyl-*N*-[4-(trifluoromethoxy)benzyl]amine (0.438 g, 2.00 mmol) and {4-[(2*S*)-2,3-diethoxy-3-oxopropyl]phenoxy}acetic acid (0.593 g, 2.00 mmol) in methylene chloride (20 mL) were added *N*,*N*-diisopropylethylamine (0.80 mL, 4.6 mmol) and *O*-(benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate (0.674 g, 2.10 mmol) and the reaction mixture was stirred at room temperature overnight. The resulting solution was diluted with methylene chloride (40 mL) and the organic phase was washed with 5% HCl (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification on a prepacked column of silica gel (Isolute® SPE Column, 50 g/150 mL) with methylene chloride/ethyl acetate 10:1 as the eluent yielded 0.57 g (58%) of a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.08–1.28 (m, 9H), 2.88–3.00 (m, 2H), 3.28–3.44 (m, 3H), 3.60 (m, 1H), 3.96 (m, 1H), 4.12–4.20 (m, 2H), 4.60 and 4.62 (2s, 2H, rotamers), 4.66 and 4.74 (2s, 2H, rotamers), 6.74 and 6.89 (2d, 2H, rotamers), 7.08–7.27 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 12.4, 14.0, 14.4, 15.2, 38.6, 41.1, 41.5, 47.5, 49.7, 61.0, 66.3, 67.7, 68.3, 80.4, 114.5, 114.6, 121.2, 121.5, 128.3, 129.5, 130.6, 130.7, 130.7, 135.6, 136.1, 148.6, 156.9, 168.1, 168.2, 172.6. (The number of peaks is larger than the number of carbons due to rotamers. Trifluorinated carbon not reported.)

(iv) (2*S*)-2-Ethoxy-3-[4-(2-{ethyl[4-(trifluoromethoxy)benzyl]amino}-2-oxoethoxy)phenyl]-propanoic acid

To a solution of ethyl (2*S*)-2-ethoxy-3-[4-(2-{ethyl[4-(trifluoromethoxy)benzyl]amino}-2-oxoethoxy)phenyl]propanoate (0.560 g, 1.13 mmol) in THF (50 mL) was added aqueous 0.10 M LiOH (25 mL) and the solution was stirred at room temperature overnight. After neutralisation with 5% HCl, the solvent volume was reduced *in vacuo* and the remaining aqueous phase was

acidified with 5% HCl and extracted with ethyl acetate (2 x 50 mL). The combined organic phase was washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification on a prepacked column of silica gel (Isolute® SPE Column, 10 g/70 mL) with ethyl acetate as the eluent afforded 0.457 g (87%) of a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.08–1.23 (m, 6H), 2.96 (m, 1H), 3.08 (m, 1H), 3.33–3.43 (m, 2H), 3.48 (m, 1H), 3.59 (m, 1H), 4.05 (m, 1H), 4.60 and 4.62 (2s, 2H, rotamers), 4.67 and 4.75 (2s, 2H, rotamers), 6.75 and 6.89 (2d, 2H, rotamers), 7.09–7.27 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 12.4, 14.0, 15.2, 37.8, 41.2, 41.6, 47.5, 49.7, 67.0, 67.6, 68.2, 79.8, 114.6, 114.8, 121.2, 121.5, 128.3, 129.5, 129.9, 130.8, 130.8, 135.4, 136.0, 148.7, 148.8, 156.9, 157.0, 168.3, 168.3, 174.2. (The number of peaks is larger than the number of carbons due to rotamers. Trifluorinated carbon not reported.)

Example 6

(2*S*)-2-Ethoxy-3-[4-(2-{ethyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]propanoic acid

(i) Ethyl (2*S*)-2-ethoxy-3-[4-(2-{ethyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl] propanoate

To a solution of *N*-ethyl-*N*-[4-(trifluoromethyl)benzyl]amine (0.213 g, 1.05 mmol) and {4-[(2*S*)-2,3-diethoxy-3-oxopropyl]phenoxy}acetic acid (0.296 g, 1.00 mmol) in methylene chloride (10 mL) were added *N*,*N*-diisopropylethylamine (0.40 mL, 2.3 mmol) and *O*-(benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate (0.337 g, 1.05 mmol) and the reaction mixture was stirred at room temperature overnight. The resulting solution was diluted with methylene chloride (90 mL) and the organic phase was washed with 5% HCl (2 x 50 mL), saturated aqueous $NaHCO_3$ (2 x 50 mL), and brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification on a prepacked column of silica gel (Isolute® SPE Column, 50 g/150 mL) with methanol (0–1% gradient) in methylene chloride as the eluent yielded 0.339 g (70%) of a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06–1.24 (m, 9H), 2.88–3.00 (m, 2H), 3.28–3.44 (m, 3H), 3.59 (m, 1H), 3.96 (m, 1H), 4.10–4.19 (m, 2H), 4.64, 4.67, and 4.74 (3s, 4H, rotamers), 6.71 and 6.88 (2d, 2H, rotamers), 7.10 and 7.17 (2d, 2H, rotamers), 7.30 (d, 2H), 7.52 and 7.57 (2d, 2H, rotamers).

^{13}C NMR (100 MHz, $CDCl_3$): δ 12.3, 13.9, 14.3, 15.1, 38.5, 41.2, 41.7, 47.8, 49.9, 60.8, 66.2, 67.6, 68.2, 80.3, 114.4, 114.5, 125.5 (m), 125.8 (m), 127.1, 128.2, 129.2–130.6 (m), 130.5, 130.6, 130.6, 141.0, 141.5, 156.6, 156.8, 168.1, 168.2, 172.5. (The number of peaks is larger than the number of carbon atoms due to rotamers. Trifluorinated carbon not reported.)

(ii) (2*S*)-2-Ethoxy-3-[4-(2-{ethyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]-propanoic acid

To a solution of ethyl (2*S*)-2-ethoxy-3-[4-(2-{ethyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl] propanoate ((0.308 g, 0.64 mmol) in acetonitrile (32 mL) was added aqueous 0.10 M LiOH (16 mL) and the solution was stirred at room temperature overnight. After neutralisation with 5% HCl, the solvent volume was reduced *in vacuo* and the remaining aqueous phase was diluted with water and aqueous 0.10 M LiOH (to a total volume of 100 mL, pH~10) and washed with diethyl ether (2 x 100 mL). The aqueous phase was acidified with 5% HCl and extracted with ethyl acetate (3 x 100 mL). The combined organic phase was washed with 5% HCl (100 mL) and brine (100 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford 0.279 g (96%) of a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08–1.24 (m, 6H), 2.88–3.12 (m, 2H), 3.34–3.47 (m, 3H), 3.61 (m, 1H), 4.02 (m, 1H), 4.66, 4.67, 4.69, and 4.76 (4s, 4H, rotamers), 6.72 and 6.89 (2d, 2H, rotamers), 7.12 and 7.19 (2d, 2H, rotamers), 7.32 (d, 2H), 7.53 and 7.58 (2d, 2H, rotamers), 8.08 (bs, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 12.3, 13.9, 15.1, 38.0, 41.4, 41.9, 48.0, 50.1, 66.8, 67.5, 68.1, 79.8, 114.5, 114.7, 125.6 (m), 125.9 (m), 127.2, 128.2, 129.2–130.6 (m), 130.2, 130.7, 130.8, 140.8, 141.3, 156.7, 156.9, 168.6, 168.6, 175.5. (The number of peaks is larger than the number of carbon atoms due to rotamers. Trifluorinated carbon not reported).

An alternative procedure for the preparation of the tert-butylamine salt of Example 6 is as follows:

(i) N-[4-(trifluoromethyl)benzyl]ethane amine

Ethylamine hydrochloride (281 g, 3.45 mol), 4-(trifluoromethyl)benzaldehyde (500 g, 2.81 mol), toluene (1250 mL) and 4M aqueous sodium hydroxide (935 mL) were charged into a reactor. The mixture was stirred for 3 hours before palladium 5% on charcoal (50% w/w paste, 25 g) was added. The mixture was stirred under 2 bar hydrogen pressure until the hydrogen consumption ceased. The solids were filtered off and the aqueous layer was discarded. The product-containing layer was used without further purification in the next step.

(ii) 2-chloro-N-ethyl-N-4-(trifluoromethyl)benzyl acetamide

To the toluene solution of N-[4-(trifluoromethyl)benzyl]ethane amine 32.4 % w/w (251.6 g, 0.40 mol), water (125 mL) and aqueous sodium hydroxide 50% w/w (47.4 g, 0.59 mol) were added. Chloroacetyl chloride (54.1 g, 0.47 mol) diluted with toluene (39.7 mL) was added over at least 30 minutes to maintain a reaction temperature below 25°C. The mixture was aged for 30 minutes, the layers were separated and the organic layer was washed with HCl 2.5M (100 mL) and then used without further purification in the next step.

(iii) Ethyl (2S)-2-ethoxy-3-[4-(2-{ethyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]propanoate

Potassium carbonate (44.4 g, 0.315 mol), ethyl (2*S*)-2-ethoxy-3-(4-hydroxyphenyl)propanoate (25.0 g, 0.105 mol), tetrabutyl ammonium bromide (0.345 g, 0,00105 mol) and toluene (34g) were charged into a reactor and aged before water (2.25 g) was added and the mixture was heated to 60°C. The toluene solution of 2-chloro-N-ethyl-N-4-(trifluoromethyl)benzyl acetamide (1.05 eq), from previous step, was added at 60°C over 30-60 minutes. The resulting mixture was stirred for several hours at elevated temperature. Water (213 g) was added and after separation, the organic layer was evaporated to dryness and the product was crystallized from ethanol (151.5 g) at 0°C by portion-wise addition of water (total 300 g). The product was collected and dried in 83% yield over 3 steps.

(iv) 2-methylpropan-2-aminium (2S)-2-ethoxy-3-[4-(2-{ethyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]propanoate

The ethyl-(2*S*)-2-ethoxy-3-[4-(2-{ethyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]propanoate (15 g, 0,0299 mol), water (37.5 mL) and ethanol (18.75 mL) were mixed and heated to 35°C. Aqueous sodium hydroxide 45% w/w (4.15 g, 0.0467 mol) was charged into the reactor. The mixture was aged one hour. The reaction mixture was acidified by addition of HCl 37% w/w (5.94 g) and the resulting mixture was extracted with butyl acetate (37.5 mL). The aqueous layer was discarded before the organic layer was dried *in vacuo*. Butyl acetate (62 mL) was added and the solution was heated to 75°C. *Tert*-butyl amine (2.84g, 0.0389 mol) dissolved in butyl acetate (27 mL) was added at elevated temperature. The mixture was seeded with 0.4% w/w of product salt at 70°C. The temperature was further lowered to 20°C before the 2-methylpropan-2-aminium (2*S*)-2-ethoxy-3-[4-(2-{ethyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]propanoate was collected, washed and dried in 88% yield.

Example 7

(2*S*)-3-[4-(2-{Butyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]-2-ethoxypropanoic acid

(i) Ethyl (2*S*)-3-[4-(2-{butyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]-2-ethoxypropanoate

To a solution of *N*-butyl-*N*-[4-(trifluoromethyl)benzyl]amine (0.486 g, 2.10 mmol) and {4-[(2*S*)-2,3-diethoxy-3-oxopropyl]phenoxy}acetic acid (0.593 g, 2.00 mmol) in methylene chloride (20 mL) were added *N*,*N*-diisopropylethylamine (0.80 mL, 4.6 mmol) and *O*-(benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate (0.674 g, 2.10 mmol) and the reaction mixture was stirred at room temperature overnight. The resulting solution was diluted with methylene chloride (80 mL) and the organic phase was washed with 5% HCl (3 x 50 mL), saturated aqueous $NaHCO_3$ (2 x 50 mL), and brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification on a prepacked column of silica gel (Isolute® SPE Column, 70 g/150 mL)

with methanol (0–1% gradient) in methylene chloride as the eluent and collection of pure fractions yielded 0.355 g (35%) of a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82–0.93 (m, 3H), 1.09–1.17 (m, 3H), 1.20 (t, 3H), 1.22–1.38 (m, 2H), 1.44–1.61 (m, 2H), 2.87–3.00 (m, 2H), 3.25–3.39 (m, 3H), 3.59 (m, 1H), 3.96 (m, 1H), 4.08–4.18 (m, 2H), 4.64, 4.68, and 4.75 (3s, 4H, rotamers), 6.72 and 6.87 (2d, 2H, rotamers), 7.10 and 7.17 (2d, 2H, rotamers), 7.29 (d, 2H), 7.51 and 7.56 (2d, 2H, rotamers).

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5, 14.0, 14.9, 19.9, 29.0, 30.5, 38.3, 45.9, 46.7, 48.1, 50.1, 60.6, 66.0, 67.3, 67.9, 80.1, 114.2, 114.3, 125.3 (m), 125.6 (m), 126.9, 127.9, 128.8–130.5 (m), 130.2, 130.3, 130.4, 141.0, 141.4, 156.5, 156.7, 168.1, 172.2. (The number of peaks is larger than the number of carbon atoms due to rotamers. Trifluorinated carbon not reported.)

(ii) (2*S*)-3-[4-(2-{Butyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]-2-ethoxy propanoic acid

To a solution of ethyl (2*S*)-3-[4-(2-{butyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy) phenyl]-2-ethoxypropanoate (0.311 g, 0.61 mmol) in acetonitrile (30 mL) was added aqueous 0.10 M LiOH (15 mL) and the solution was stirred at room temperature overnight. After acidification with 5% HCl, the mixture was extracted with ethyl acetate (3 x 100 mL) and the combined organic phase was washed with 5% HCl (100 mL) and brine (100 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford 0.232 g (79%) of a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84–0.94 (m, 3H), 1.10–1.19 (m, 3H), 1.20–1.36 (m, 2H), 1.46–1.62 (m, 2H), 2.87–3.10 (m, 2H), 3.25–3.45 (m, 2H), 3.61 (m, 1H), 4.01 (m, 1H), 4.66, 4.69 and 4.76 (3s, 4H, rotamers), 6.72 and 6.88 (2d, 2H, rotamers), 7.12 and 7.19 (2d, 2H, rotamers), 7.30 (d, 2h), 7.53 and 7.59 (2d, 2H, rotamers), 8.27 (bs, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 15.1, 20.1, 29.2, 30.7, 38.0, 46.3, 47.0, 48.4, 50.4, 66.7, 67.4, 68.1, 79.8, 114.5, 114.6, 125.6 (m), 125.9 (m), 127.1, 128.2, 129.2–130.5 (m), 130.2, 130.7, 130.8, 140.8, 141.2, 156.7, 156.9, 168.8, 175.6. (The number of peaks is larger than the number of carbon atoms due to rotamers. Trifluorinated carbon not reported.)

Example of preparation of a *tert*-butylamine salt of (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid

(2*S*)-2-Ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid (0,49 g) and *tert*-butylamine (0,077 g) were mixed in acetone(8 ml/g), followed by addition of isooctane (8 ml/g) and stirred at room temperature. The product (0.36 g) was filtered off and washed with isooctane (4 ml/g) and was dried in room temperature. The product was confirmed with NMR and XRPD.

^{1}H-NMR (400 MHz, $CDCl_3$):
7.3-7.0 (7H, m), 6.7 (1H, d), 6.6 (1H, d), 4.6 (1H, s), 4.3 (1H, s), 3.7 (1H, m), 3.6 (1H, m), 3.5 (2H, m), 3.3 (1H, t), 3.1 (2H, m), 2.9 (1H, m), 2.7 (3H, m), 1.5 (2H, br m), 1.3 (9H, br s), 1.2 (6H, br s), 1.0 (3H, t), 0.8 (3H, m)

Examples of properties of *tert*-butylamine salt of (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid

DSC showed an endotherm with an extrapolated onset temperature of 107°C. TGA showed a weight loss of 12.7% w/w between 102-236°C. DSC analysis repeated on purer sample may give a higher melting point. Crystals of *tert*-butylamine salt of (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid (obtained by way of the example above) were analyzed by XRPD and the results are tabulated below and are shown in Figure 1. In Figure 1, the d-values and intensities are as follows:

d-value (Angstrom)	intensity (rel)
18.7	vs
11.5	m
10.4	w
8.7	w
8.1	m
7.3	m
6.9	m
6.7	w
6.3	w
5.9	s
5.8	m
5.5	s
5.2	w
5.1	w
5.00	w
4.86	w
4.71	s
4.44	w
4.24	m
4.08	s
4.02	w
3.77	m
3.74	w
3.67	w
3.53	w
3.14	w
3.06	w

Examples of granulation and compression of tablets

Tablets comprising (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid are manufactured using wet granulation, compression and film coating processes:

Firstly, *tert*-butylamine salt of (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid, mannitol and sodium starch glycollate are mixed together using a wet high shear granulater to produce a uniform distribution of the drug substance. Purified water is added to the powders with further mixing until a wet mass is formed. The wet mass is passed through a screening mill and the resultant granules dried to an appropriate, about equal to or less than 2 %, moisture content, using a direct heating, fluidized solid bed (fluid bed drier). Magnesium stearate is added to the dry granules, which are then passed through a screening mill prior to blending. The blended granules are compressed into tablet cores using a tablet press. The compressed cores are then coated with an aqueous suspension of film coating components using perforated drum coater.

COMPONENTS	PROCESS	IN-PROCESS CONTROLS
Example 1 →	**STAGE 1: DRY MIX**	
Mannitol	↓	
Sodium starch glycollate →	**STAGE 2: DRY MIX**	
Mannitol	↓	
Purified water →	**STAGE 3: WET MIX**	
	↓	
	STAGE 4: WET GRANULATION	
	↓	
	STAGE 5: DRYING	Moisture content
	↓	
Magnesium stearate →	**STAGE 6: DRY GRANULATION**	
	↓	
	STAGE 7: BLENDING	Appearance
	↓	Core weight
	STAGE 8: COMPRESSION	Hardness
Hypromellose 2910	↓	Thickness
Macrogol 400		Friability
Titanium dioxide		Disintegration time
Yellow iron oxide →		
Red iron oxide		
Black iron oxide		
Purified water		
	STAGE 9: COATING	Appearance

Description of the tablets

The drug product consists of a matched series of plain, round, 6 mm diameter, biconvex, beige film-coated tablets containing 0.1, 0.5, 2.5 and 12.5 mg of (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid (expressed as free acid).

Composition

The quantitative compositions of the (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid 0.1, 0.5, 2.5 and 12.5 mg film-coated tablets are presented.

Table 1 - Composition of (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid (Example 1) 0.1, 0.5, 2.5 and 12.5 film-coated tablets.

As used below:

Example 1 means (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid, free acid

Example 1 TBA means (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid, tert-Butylammonium[a]

Tablet strength	**0.1 mg**	**0.5 mg**	**2.5 mg**	**12.5 mg**	**Function**	**Reference to standards**
Formulation reference	**F13309**	**F13311**	**F13313**	**F13315**		
Ingredient	**mg/tablet**	**mg/tablet**	**mg/tablet**	**mg/tablet**		
Tablet core						
Example 1 TBA	0.116	0.580	2.900	14.500	Drug substance	This document
Mannitol	93.884	93.420	91.100	79.500	Diluent	Ph Eur
Sodium starch glycollate	4.000	4.000	4.000	4.000	Disintegrant	Ph Eur
Magnesium stearate	2.000	2.000	2.000	2.000	Lubricant	Ph Eur
Purified water[b]	qs	qs	qs	qs	Granulating fluid	Ph Eur
Core tablet weight	100 mg	100 mg	100 mg	100 mg		
Tablet coating						
Hypromellose 2910[c]	1.438	1.438	1.438	1.438	Film-former	Ph Eur

Titanium dioxide[c]	0.685	0.685	0.685	0.685	Opacifier	Ph Eur E171 CI[77891]
Macrogol 400[c]	0.144	0.144	0.144	0.144	Plasticiser	Ph Eur
Yellow iron dioxide[c]	0.026	0.026	0.026	0.026	Colouring agent	E172 CI[77492]
Red iron oxide[c]	0.006	0.006	0.006	0.006	Colouring agent	E172 CI[77491]
Black iron oxide[c]	0.002	0.002	0.002	0.002	Coluring agent	E172 CI[77499]
Purified water[b]	qs	qs	qs	qs	Solvent	Ph Eur
Nominal coated weight	102.3 mg	102.3 mg	102.3 mg	102.3 mg		

1.16 mg of Example 1 TBA is equivalent to 1.0 mg of Example 1 (0.116 mg Example 1 TBA = 0.1 mg Example 1, 0.58 mg Example 1 TBA = 0.5 mg Example 1, 2.9 mg Example 1 TBA = 2.5 mg Example 1 and 14.5 mg Example 1 TBA = 12.5 mg Example 1).

[b] Purified water is used as the granulating fluid during the manufacture of the tablet core and is removed during granule drying. Purified water is also used as the solvent/carrier fluid during film coating of the tablets and is removed during the coating process.

[c] The hypromellose 2910, titanium dioxide, macrogol 400, yellow iron oxide, red iron oxide and black iron oxide may be applied using proprietary coating products (eg, Opadry Beige 03B27164 supplied by Colorcon Ltd or equivalent).

Characterisation of the composition

Tablets of (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid were analysed to verify the actual tert-butylammonium (TBA) content in the tablets. Tablets containing 12.5mg and 2.5mg of the active ingredient were analysed.

Method

Sample: (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic 2.5mg tablets, were used.

8 tablets were crushed using a pestle and mortar and placed in a glass vial, 2ml $CDCl_3$ was added and mixed well. The suspension was filtered through a 0.45μm PTFE filter and approximately 1ml filtrate used for NMR analysis.

The analysis was carried out in duplicate.

Relative TBA content is calculated by comparing the integration of the TBA protons to known protons from the (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid molecule and calculating the TBA content relative to (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic itself.

Results:

Replicate 1 = 52.8% relative TBA content
Replicate 2 = 52.8% relative TBA content

Average = 53% relative TBA content

The 2.5mg tablets show an approximate 40% loss in TBA counter-ion content, and there is therefore about 50% of the (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic in the tablet present as (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic free acid, and 50% present as the TBA salt.

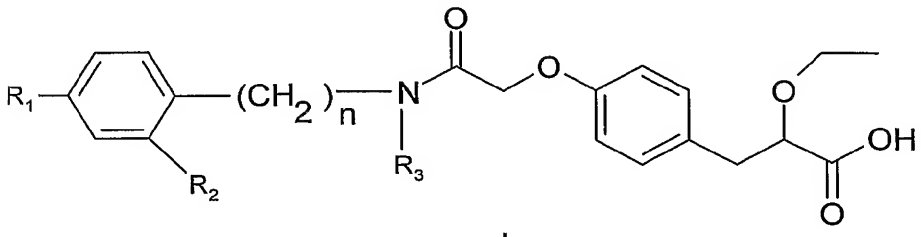
It is proposed as the loss of TBA counter-ion will be more pronounced in the lower dosage tablets. The reasoning behind this is that (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic TBA salt is very soluble in water (>200 mg/ml), and can

therefore dissolve in the granulating fluid (water) during wet granulation. For the 12.5mg tablets, there is not enough water present to dissolve all the drug, for the 2.5mg tablets and also for lower strength tablets (0.1 and 0.5 mgs) there is sufficient water to dissolve all the drug (subject to excipients competing for the water): It is believed that (2S)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid TBA salt when dissolved in the granulating fluid may "coat" the excipients.

Example spectrum of an (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid (Example 1) film coated tablet in $CDCl_3$ is given in Figure 2.

Claims

1. A pharmaceutical composition comprising a compound of formula (I)



I

wherein n is 1 or 2, R^1 represents hydrogen, chloro, trifluoromethyl or trifluoromethoxy, R^2 represents hydrogen or fluoro and R^3 represents a C_{2-6}alkyl group, wherein the compound of formula (I) is present in the composition as a free acid and as a *tert*-butyl amine salt thereof.

2. A pharmaceutical composition according to claim 1, wherein the amount of the *tert*-butylamine salt is equal to or below 95% of the total amount the compound of formula (I).

3. A pharmaceutical composition according to claim 1, wherein the amount of the *tert*-butylamine salt is equal to or below 50% of the total amount the compound of formula (I).

4. A pharmaceutical composition according to any of the claims 1-3, wherein n is 1 or 2 and R_1 and R_2 are hydrogen and R_3 is C_6H_{13}.

5. A pharmaceutical composition according to any of the claims 1-3, wherein n is 1, R_1 represents chloro, trifluoromethyl or trifluoromethoxy, R_2 represents hydrogen or fluoro and R_3 represents a C_{2-4}-alkyl group.

6. A pharmaceutical composition according to any of the claims 1-5, comprising a compound choosen from the following:
(2*S*)-2-Ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid;
(2*S*)-3-(4-{2-[Benzyl(hexyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid;
(2*S*)-3-[4-(2-{Butyl[2-fluoro-4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]-2-ethoxypropanoic acid;
(2*S*)-3-(4-{2-[(4-Chlorobenzyl)(ethyl)amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid;

(2*S*)-2-Ethoxy-3-[4-(2-{ethyl[4-(trifluoromethoxy)benzyl]amino}-2-oxoethoxy)phenyl]-propanoic acid;

(2*S*)-2-Ethoxy-3-[4-(2-{ethyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl] propanoic acid; and

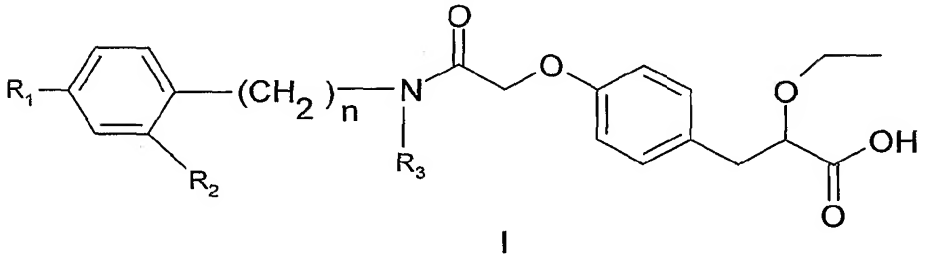
(2*S*)-3-[4-(2-{Butyl[4-(trifluoromethyl)benzyl]amino}-2-oxoethoxy)phenyl]-2-ethoxypropanoic acid

as a free acid and as a *tert*-butyl amine salt thereof.

7. A pharmaceutical composition according to any of the claims 1-6, wherein the dosage form is an oral formulation.

8. A pharmaceutical composition according to claim 7, wherein the dosage form is a solid or semi-solid oral formulation.

9. A process for preparing a pharmaceutical composition comprising a *tert*-butyl amine salt of a compound of formula (I) as well as free acid of the compound:



I

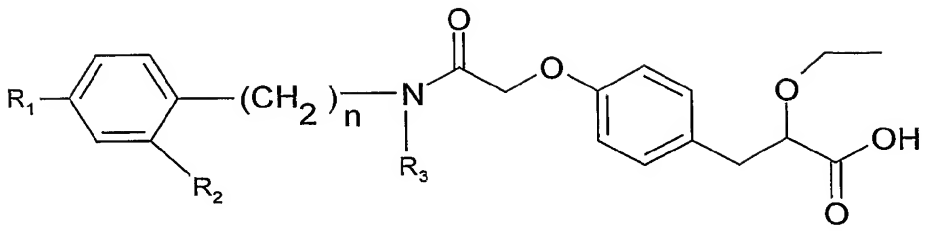
wherein n is 1 or 2, R^1 represents hydrogen, chloro, trifluoromethyl or trifluoromethoxy, R^2 represents hydrogen or fluoro and R^3 represents a C_{2-6}alkyl group,

comprising the steps of:

a) granulating a *tert*-butyl amine salt of a compound of formula (I);

b) drying the granules.

10. A process for preparing tablets including a pharmaceutical composition comprising a *tert*-butyl amine salt of a compound of formula (I) as well as free acid of the compound:



I

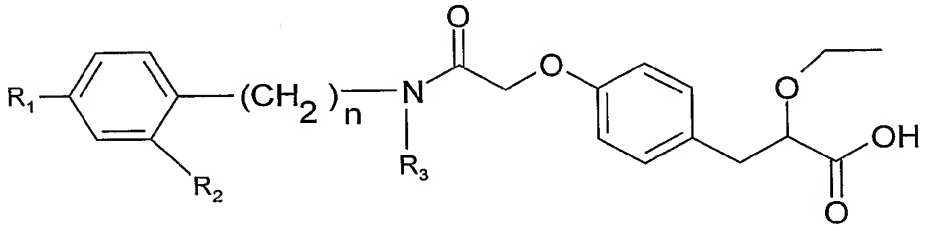
wherein n is 1 or 2, R^1 represents hydrogen, chloro, trifluoromethyl or trifluoromethoxy, R^2 represents hydrogen or fluoro and R^3 represents a C_{2-6}alkyl group,

comprising the steps of:

a) blending a tert-butyl amine salt of a compound of formula (I) with excipients;

b) compressing the blend into tablets.

11. A process for preparing tablets including a pharmaceutical composition comprising a *tert*-butyl amine salt of a compound of formula (I) as well as free acid of the compound:



I

wherein n is 1 or 2, R^1 represents hydrogen, chloro, trifluoromethyl or trifluoromethoxy, R^2 represents hydrogen or fluoro and R^3 represents a C_{2-6}alkyl group,

comprising the steps of:

a) preparing tablets comprising the salt;

b) coating the tablets.

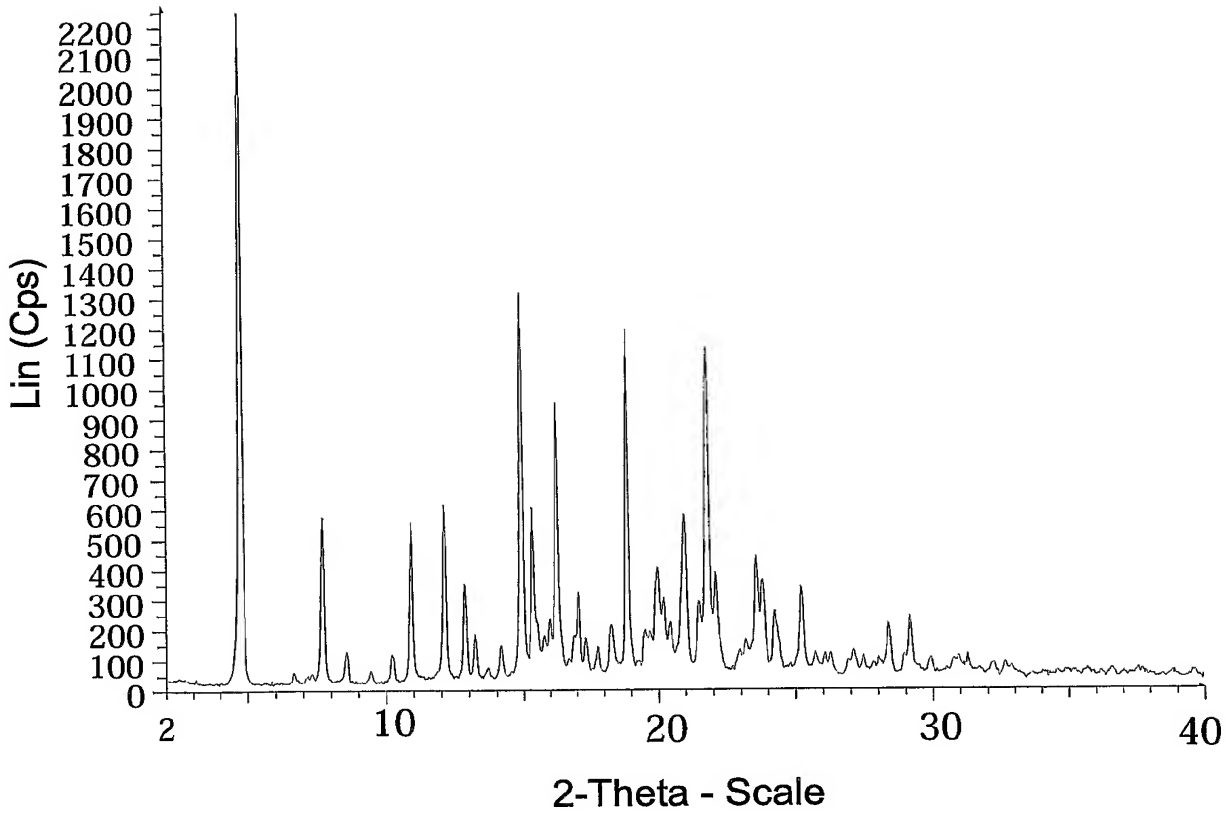


Figure 1,

XRPD pattern of tert-butylamine salt of (2S)-2-ethoxy-3-(4-{2-[hexyl (2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid

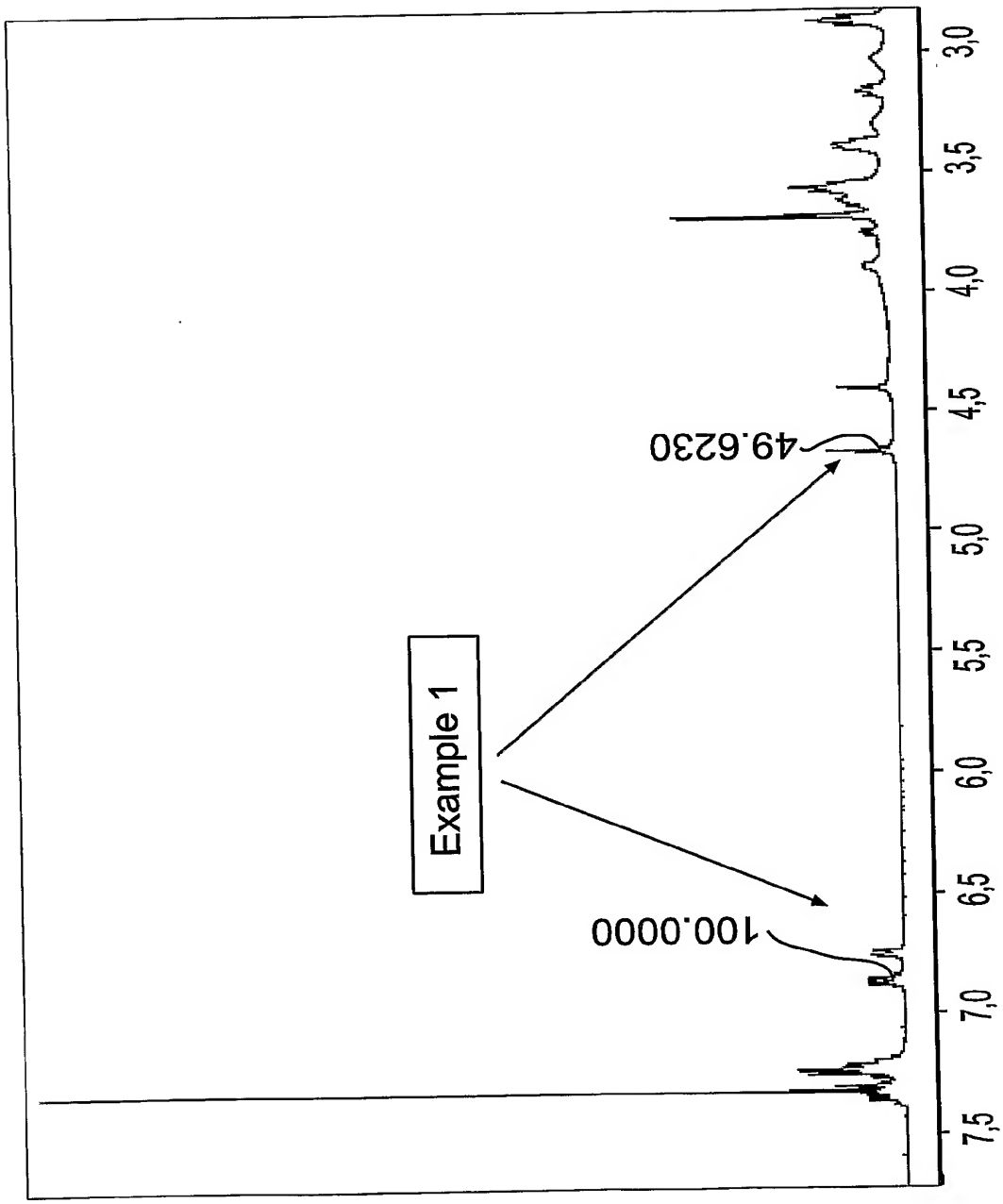


Figure 2.

Example spectrum of an (2S)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid (Example 1) film coated tablet in $CDCl_3$

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2006/000864

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, CHEM ABS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004110984 A1 (ASTRAZENECA AB), 23 December 2004 (23.12.2004) --	1-10
X	WO 2004056748 A1 (ASTRAZENECA AB), 8 July 2004 (08.07.2004) --	1-10
X	WO 03051821 A1 (ASTRAZENECA AB), 26 June 2003 (26.06.2003) --	1-10
A	WO 2004110985 A1 (ASTRAZENECA AB), 23 December 2004 (23.12.2004) --	1-10

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 October 2006	17 -10- 2006
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Eva Johansson/MP Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2006/000864

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004110982 A1 (ASTRAZENECA AB), 23 December 2004 (23.12.2004) -- --------	1-10

International patent classification (IPC)

A61K 31/195 (2006.01)
A61K 31/205 (2006.01)
A61K 9/20 (2006.01)
A61P 3/10 (2006.01)

Download your patent documents at www.prv.se
The cited patent documents can be downloaded at www.prv.se by following the links:

- In English/Searches and advisory services/Cited documents (service in English) or
- e-tjänster/anförda dokument (service in Swedish).

Use the application number as username.
The password is **DJHHOFPBBP**.

Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.

INTERNATIONAL SEARCH REPORT
Information on patent family members

04/03/2006

International application No.
PCT/SE2006/000864

WO	2004110984	A1	23/12/2004	AU	2004247610	A	23/12/2004
				BR	PI0411525	A	01/08/2006
				CA	2528932	A	23/12/2004
				CN	1809529	A	26/07/2006
				EP	1638922	A	29/03/2006
				GB	0314129	D	00/00/0000
				IS	8231	A	13/01/2006
				NO	20055922	A	06/01/2006
				US	20060142389	A	29/06/2006
WO	2004056748	A1	08/07/2004	AU	2003290309	A	14/07/2004
				BR	0317458	A	16/11/2005
				CA	2508851	A	08/07/2004
				CN	1753862	A	29/03/2006
				EP	1572626	A	14/09/2005
				GB	0229931	D	00/00/0000
				IS	7946	A	19/07/2005
				JP	3786945	B	21/06/2006
				JP	2006045240	A	16/02/2006
				JP	2006511572	T	06/04/2006
				MX	PA05006812	A	08/09/2005
				NO	20052914	A	19/07/2005
				RU	2005117792	A	27/01/2006
				US	20050131068	A	16/06/2005
				US	20050282822	A	22/12/2005

INTERNATIONAL SEARCH REPORT
Information on patent family members

04/03/2006

International application No.
PCT/SE2006/000864

WO	03051821	A1	26/06/2003	AU	2002352427	A	00/00/0000
				AU	2002366315	A	00/00/0000
				BR	0214986	A	14/12/2004
				BR	0214988	A	14/12/2004
				CA	2469302	A	26/06/2003
				CA	2470491	A	26/06/2003
				CN	1620422	A	25/05/2005
				CN	1620423	A	25/05/2005
				EP	1458672	A	22/09/2004
				EP	1458673	A	22/09/2004
				HU	0402022	A	28/01/2005
				HU	0402133	A	28/02/2005
				IL	162330	D	00/00/0000
				IL	162331	D	00/00/0000
				JP	3784804	B	14/06/2006
				JP	2005336209	A	08/12/2005
				JP	2005526011	T	02/09/2005
				JP	2005526704	T	08/09/2005
				MX	PA04006003	A	27/09/2004
				MX	PA04006004	A	27/09/2004
				NO	20043023	A	15/07/2004
				NO	20043164	A	16/07/2004
				NZ	533274	A	23/12/2005
				NZ	533276	A	28/04/2006
				PL	370672	A	30/05/2005
				PL	370673	A	30/05/2005
				RU	2004116917	A	10/11/2005
				RU	2004116918	A	10/11/2005
				SE	0104334	D	00/00/0000
				US	20050113362	A	26/05/2005
				US	20050171204	A	04/08/2005
				US	20050282822	A	22/12/2005
				WO	03051822	A	26/06/2003
				ZA	200404657	A	29/08/2005
WO	2004110985	A1	23/12/2004	AU	2004247611	A	23/12/2004
				BR	PI0411455	A	18/07/2006
				CA	2527608	A	23/12/2004
				EP	1638921	A	29/03/2006
				GB	0314136	D	00/00/0000
				IS	8232	A	13/01/2006
				NO	20055923	A	06/01/2006
WO	2004110982	A1	23/12/2004	AU	2004247612	A	23/12/2004
				BR	PI0411558	A	01/08/2006
				CA	2528933	A	23/12/2004
				CN	1809528	A	26/07/2006
				EP	1638920	A	29/03/2006
				GB	0314134	D	00/00/0000
				MX	PA05013715	A	08/03/2006
				NO	20055924	A	05/01/2006
				US	20060142392	A	29/06/2006